Evolution of the Benzodiazepine Prescriptions by Primary care Physicians in Flanders: A registry-based study

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Abstract

Aims

The aim of the present study was to describe the trends in benzodiazepine prescription rates by general practitioners between 2000 and 2015 in the Dutch-speaking part (Flanders) of Belgium.

Methods

For the purpose of this work, data from Intego project were used. Intego is a computerized morbidity registration network based on data provided by general practitioners in the Flanders region of Belgium. The annual benzodiazepine prescription rates among adults (≥18 years) during the 15-year study period were calculated in total study population and different age groups: 18-44-, 45-64- and >64 years old. Analysis was done separately for short- (< 3 prescription per year) and long term users (≥ 3 prescription per year). To analyze the trend in gender- and age-standardized prevalence rates between 2000 and 2015, we performed a joinpoint regression analysis.

Results

In 2000, 2234 patients (2, 8 %) received ≥ 3 prescriptions. This was increased to 3930 patients (3, 9 %) in 2015 corresponding to an increase of 1.1 % in benzodiazepine prescription rate between 2000 and 2015. Joinpoint trends analysis for benzodiazepine prescription rates throughout the 15-years study period showed different prescription trends in different age and gender groups for both short- and long-term users of benzodiazepines. In long term users in the entire study period we observed a pronounced increase in prescription rates in men younger than 45 years old (AAPC=APC= 4.5, 95% CI= 3.0; 6.0). In the 45–64 years age group we also found a significant increase in prescription rates although smaller than that in the younger males of <45 years old. (AAPC=APC= 0.9, 95% CI: 0.1; 1.7).

In contrast to younger males there was a decreased trend in females younger than 45 years old (AAPC=APC= -1.6, CI: -2.3; -0.9). However, we found a dichotomous trend independent of gender in the older adults of ≥ 65 years old. The first trend, which was observed between 2000 and 2007, showed a pronounced increase (APC= 5.6, 95% CI: 3.6; 7.7), whereas the second trend showed a slight drop (APC=-2.6, 95% CI: -3.9; -1.3) that was observed afterwards (between 2006-2007 and 2015).

Relatively high percentages of the long term use of benzodiazepines were associated with back pain and depression (48% and 29% respectively in 2015). Opioids and antidepressants were co-prescribed the most with benzodiazepines (45% for each in 2015).

Conclusions

Overall prevalence of long term use of benzodiazepines increased slightly during the-15 years study period. Different age and gender groups, however, showed different prescription trends. A large proportion of the long term use of benzodiazepines was associated with back pain and depression, consistent with a larger proportion of co-prescribing opioids and antidepressants with benzodiazepines. Our findings point at the need to address the issue of increased long term use of benzodiazepines.

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Introduction

Benzodiazepines (BDZs) are molecules with known hypnotic/sedative and anxiolytic properties. They exert their effect via interaction with their gamma-amino butyric acid (GABA) receptors in the human brain [1]. There are different subtypes of benzodiazepine receptors for which different BDZs show different affinities leading to difference in observed clinical effect among BDZs [2]. It seems that the different subtypes correlate with various pharmacological effects of the BDZs. Therefore, it is not surprising that BDZs have a wide range of potential therapeutic indications including insomnia, anxiety/panic disorders, seizures, and muscle spasms[3]. Despite benefits from the appropriate short term use of the BDZs in a variety of neuropsychiatric conditions, on long term use they are associated with serious health problems with drug dependence as the most recognized risk [4]. It has also been documented that long term use of BDZs is associated with cognitive impairment, fall risk and resultant hip fractures, insomnia, and memory disorders especially in older populations [4 5 6 7 8 9 10 11 12 13].

Increased mortality has also been found by a recent meta-analysis of 2,350,093 subjects using BDZs[14]. Increased BDZs prescription can also result in misuse of these medications. For all these reasons different guidelines recommend only short term prescription of the BDZs if needed. Despite this, the long term prescription of BDZs has been documented widely among different clinicians including general practitioners [1 5 15 16 17]. Different studies have shown that BDZs were mostly prescribed for longer periods by general practitioners to treat insomnia and anxiety in particular in older population[18]. However, none of the current guidelines recommend benzodiazepine as first-line treatment for both insomnia and anxiety[19].

The aim of the present work was to describe the trends in benzodiazepine prescription rates by general practitioners during the 15-years study period (2000-2015) in the Dutch-speaking part (Flanders) of Belgium using a large registered database. We also aimed to study the indications for which BDZs were prescribed by general practitioners. We further investigated evolution in co-prescribing benzodiazepines with other central nervous system (CNS) affecting medications including opioids and Z-drugs because of the increased morbidity resulting from those co-prescriptions. Elucidating (co)prescribing patterns of benzodiazepines as well as indications for can help us to better understand and as a result to address the issue of increased inappropriate use of benzodiazepines and their consequent complications.

Materials and methods

Data Source

For the purpose of this thesis, data from Intego project were used. Intego which stands for "integrated computerized network" was established by the department of general practice of the KU Leuven in 1990[20]. The source of Intego data is information provided by a network of about 100 general practitioners. Those general practitioners work in around 50 practices with an optimal registration performance in the Flanders region of Belgium[20]. Data provided by those practices are collected during their daily practices and contain some demographic, clinical and biomedical information (such as age, gender, weight, height, blood pressure and (new) diagnosis), laboratory tests, and electronic prescribed medications among others. Data registration occurs with use of computer-generated keywords in a predetermined field in the electronic health record[20]. Each keyword is associated with a unique program-specific internal code and can be linked to classifications as International Classification of Primary Care (ICPC-2) for diagnosis, and WHO's Anatomical Therapeutic Chemical (ATC) for medications.

The ethical committee of the Catholic University Leuven medical school and the Belgian Privacy Commission approved the Intego procedure (protocol number ML 1723 and SCSZG/13/079 respectively).

Study population and design

Intego database between January 1, 2000 and December 31, 2015 was used in this study. We selected patients aged 18 years and above who had been continuously enrolled in the Intego database.

Short-term benzodiazepine users were defined as those who received < 3 benzodiazepine prescriptions per year. Patients who received ≥ 3 prescriptions in one year were called long-term users of BDZs.

Data on the patients' demographic characteristics (age group and gender), indication for benzodiazepine prescription (insomnia, anxiety, back pain, neurologic, depression), co-morbidities (social/psychiatric and physical), and concomitant prescribed medications (opioids, antidepressants, antipsychotics and Z-drugs) were collected for both 2000 and 2015. BZDs are defined as the ATC classifications N05BA and N05CD.

Data analysis

A repeated cross-sectional analysis, using Chi-square trend test, was conducted for 2 time periods (2000 and 2015) to investigate the general changes in the benzodiazepine prescription rates among adults (aged18 years and above), the indications for which BDZs were prescribed and CNS-affecting medications co-prescribed with BDZs.

The annual benzodiazepine prescription rates during a 15 year-study period were also calculated in total study population and different age groups and genders: 18-44-, 45-64- and >64 years old. Analysis was done separately for short- and long-term users. For that

purpose we performed a joinpoint regression analysis which is one of the most common and well-known methods for identifying and studying statistically significant changes in course of a variable over time. In this method, we first find the points where the variable has undergone significant changes. These points are called joinpoints. We then approximate the regression function between the two consecutive joinpoints. To perform joinpoint analysis, we need at least four observations between two joinpoints or three observations to the end of the database. Having joinpoints recognized, we are able to calculate two sets of parameters: the annual percentage change and the average annual percentage changes. The annual percentage change or briefly APC is computed for each significant trend. The estimated average of APC per significant trend weighted by the corresponding trend length is called average annual percentage changes or briefly AAPC. We used SEER*Stat package form the Surveillance Research Program of the US National Cancer Institute to perform joinpoint regression analysis.

Results

Cross-sectional analysis of short- and long-term benzodiazepine use

The results of the analysis of short- and long-term benzodiazepine use in general, by age group, gender, indication, and co-prescriptions with other CNS affective medication for the two time periods (2000 and 2015) are presented in Table 1. Overall we observed no change in short-term benzodiazepine prescription rates between 2000 (n= 4085, 3%) and 2015 (n=5284, 3%). Stratified by age-group, however, we observed different prescription patterns

Table 1. Serial cross-sectional analysis of short- and long-term benzodiazepine use, indications for and concomitant use of benzodiazepines with other sedative/hypnotics in 2000 and 2015

	< 3 Benzodiazepine prescriptions			**≥ 3 Benzodiazepine prescriptions**		
Characteristic						
	2000	**2015**	**P**	**2000**	**2015**	**P**
Total no of patients	4085	5284		2234	3930	
Age Years						
18-44	1068(26%)	1579(30%)	<0.001	281(13%)	502(13%)	0.8249
45-64	1517(37%)	1949(37%)	0.803	889(40%)	1338(34%)	<0.001
>64	1500(37%)	1756(33%)	<0.001	1064(48%)	2090(53%)	<0.001
Gender						<0.001
Males	1493(37%)	2123(40%)	<0.001	729(33%)	1418(36%)	0.0062
Females	2592(63%)	3161(60%)	<0.001	1505(67%)	2512(64%)	0.0062
Comorbidity/indication						
Insomnia	192(5%)	587(11%)	<0.001	149(7%)	534(14%)	<0.001
Anxiety	136(3%)	261(5%)	<0.001	108(5%)	267(7%)	0.0019
Depression	771(19%)	1066(20%)	0.116	592(26%)	1142(29%)	0.031
Neurologic	315(8%)	558(11%)	<0.001	0(9%)	577(15%)	<0.001
Dementia	23(1%)	76(1%)	<0.001	17(1%)	64(2%)	0.0058
Psychiatric problem	229(6%)	522(10%)	<0.001	172(8%)	521(13%)	<0.001
Social problems	9(0%)	80(2%)	<0.001	4(0%)	124(3%)	<0.001
Cancer	196(5%)	599(11%)	<0.001	140(6%)	645(16%)	<0.001
Backpain	1152(28%)	2221(42%)	<0.001	728(33%)	1873(48%)	<0.001
Alcohol-drugs	89(2%)	211(4%)	<0.001	54(2%)	288(7%)	<0.001
Concomitant medications						
Opioids	868(21%)	1773(34%)	<0.001	678(30%)	1776(45%)	<0.001
Anti-depressants	1103(27%)	1469(28%)	0.3897	865(39%)	1763(45%)	<0.001
Antipsychotics	386(9%)	349(7%)	<0.001	289(13%)	518(13%)	0.78
Z-drugs	218(5%)	458(9%)	<0.001	137(6%)	395(10%)	<0.001
Other hypnotics and	1141(28%)			856(38%)	1492(38%)	0.78

with an increasing trend in the younger age group of < 45 years old in 2015 (n=1579, 30%) compared with that in 2000 (n=1068, 26%, P<0.001). In 2015 a decrease was found in the prescription rates in the older adults of > 64 years old (1756=33%) in comparison to that in 2000 (1500=37%, P <0.001) (table 1).

Regarding the long-term users, our data showed that in 2000, 2234 patients (2, 8 %) received ≥ 3 prescriptions. This was increased to 3930 patients (3, 9 %) in 2015 corresponding to an increase of 1.1 % in benzodiazepine prescription rate between 2000 and 2015. Unlike in the short-term users, in long term users the older age group of > 64 years old showed an increase of 5% in the use of BDZs between 2000 and 2015 (n=1064, 48% in 2000 vs n=2090, 53% in 2015, p <0.001) (table1). Indeed, older people aged 65 and above made up relatively a higher percentage of the long-term users in both 2000 and 2015. In the middle-aged (45-65 years old) population we observed a significant decrease of 6% in the prescription rate in 2015 (n=889, 40% in 2000 vs n=1338, 34% in 2015, p <0.001).

With respect to the gender difference in both short- and long-term benzodiazepine uses we found that females made up relatively a high percentage of the short- and long-term users in both 2000 and 2015. Despite this, the prescription rates in females decreased in 2015 (n=1505, 67% in 2000 vs n=2512, 64% in 2015 for long-term users, p<0.006) meaning that in 2015, in terms of population composition, fewer women consumed BDZs than men.

Joinpoint trends analysis for benzodiazepine prescription rates

Investigating the trends in gender- and age-standardized rates between 2000 and 2015 by means of join point regression analysis we found different trends in different age categories and genders for both short- and long-term users of BDZs (table 2, fig1a,1b) indicating the effect of methodology on the obtained results.

Table 2. Age-and gender-standardized short and long term BDZs prescription rates between 2000 and 2015 by joinpoint regression analysis

Group	Summary	Trend 1		Trend 2	
	AAPC	Years	APC	Years	APC
Medications					
Benzo < 3	-0.7[-2.3;0.9]	2000-2015	-0.7[-2.3;0.9]		
Overall 18_44	1.3[0.0;2.6]	2000-2012	**-1.2[-2.1;-0.4]**	2012-2015	**11.9[4.9;19.4]**
Overall 45_64	-0.7[-1.7;0.3]	2000-2012	**-2.1[-2.7;-1.5]**	2012-2015	5.2[-0.1;10.7]
Overall 65_plus	**-1.1[-1.6;-0.7]**	2000-2015	**-1.1[-1.6;-0.7]**		
Males	-0.4[-1.7;1.0]	2000-2015	-0.4[-1.7;1.0]		
Males 18_44	**2.2[0.5;4.0]**	2000-2012	-0.5[-1.6;0.7]	2012-2015	**13.7[4.4;23.9]**
Males 45_64	**-0.1[-1.0;0.9]**	2000-2012	**-2.0[-2.6;-1.4]**	2012-2015	**8.0[3.0;13.2]**
Males 65_plus	**-0.8[-1.3;-0.3]**	2000-2015	**-0.8[-1.3;-0.3]**		
Females	-1.0[-2.5;0.5]	2000-2015	-1.0[-2.5;0.5]		
Females 18_44	0.6[-1.0;2.1]	2000-2012	**-1.7[-2.7;-0.8]**	2012-2015	**10.4[2.2;19.2]**
Females 45_64	-1.1[-2.4;0.2]	2000-2012	**-2.2[-3.0;-1.4]**	2012-2015	3.4[-3.3;10.7]
Females 65_plus	**-1.2[-1.7;-0.7]**	2000-2015	**-1.2[-1.7;-0.7]**		
Benzo >= 3	0.2[-2.8;3.3]	2000-2015	0.2[-2.8;3.3]		
Overall 18_44	**2.5[1.7;3.4]**	2000-2015	**2.5[1.7;3.4]**		
Overall 45_64	**-0.7[-1.4;-0.1]**	2000-2015	**-0.7[-1.4;-0.1]**		
Overall 65_plus	**1.1[0.1;2.2]**	2000-2007	**5.6[3.6;7.7]**	2007-2015	**-2.6[-3.9;-1.3]**
Males	0.7[-1.7;3.2]	2000-2015	0.7[-1.7;3.2]		
Males 18_44	**4.5[3.0;6.0]**	2000-2015	**4.5[3.0;6.0]**		
Males 45_64	**0.9[0.1;1.7]**	2000-2015	**0.9[0.1;1.7]**		
Males 65_plus	**0.9[0.0;1.8]**	2000-2007	**5.5[3.8;7.2]**	2007-2015	-3.0[-4.0;-1.9]
Females	0.3[-2.4;3.1]	2000-2015	0.3[-2.4;3.1]		
Females 18_44	0.8[0.0;1.7]	2000-2015	0.8[0.0;1.7]		
Females 45_64	**-1.6[-2.3;-0.9]**	2000-2015	**-1.6[-2.3;-0.9]**		
Females 65_plus	**1.6[0.4;2.9]**	2000-2006	**7.0[3.9;10.2]**	2006-2015	**-1.8[-3.1;-0.5]**

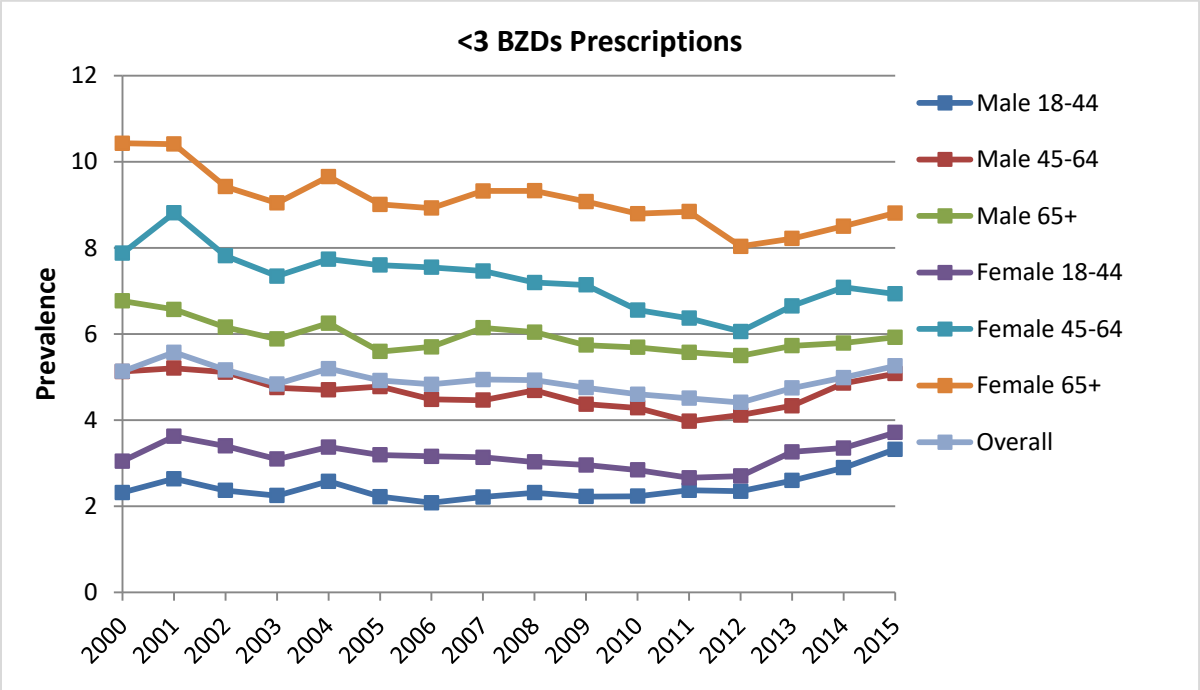
Short-term users

Analyzing the gender- and age-standardised trends for those who received <3 prescriptions for BDZs showed a small but significant decrease in younger (18-44 years) females over the first 12 years (2000-2012) of the study period (APC= -1.7, 95% CI: -2.7; -0.8) (table 2). However, afterward in the second part of the study period (2012-2015) we observed a strong significant increase (APC= 10.4, 95% CI: 2.2; 19.2) in the prescription rates. In the younger males this increasing trend was even more pronounced after 2012 (APC= 13.7, 95% CI: 4.4; 23.9). In the middle age group (45-64 years) males, but not females, we observed the same dichotomous decreasing/increasing pattern as those observed in younger males (APC 2000-2012 = -2.0, 95% CI: -2.6; -1.4) and APC 2012-2015= 8.0, 95% CI: 3.0; 13.2). We observed a gender independent decrease in benzodiazepine prescription rates in those aged > 64 years between 2000 and 2015 (APC= -0.8, 95% CI: -1.3; -0.3, APC= -1.2, CI: -1.7; -0.7 for males and females respectively). Despite this very small decreasing trend, this latter group, especially the females, had a very high prevalence of BDZs use in the entire study period (Figure 1a) (the highest prevalence of 10.4 % in 2000).

Long-term users

Age-standardized long term benzodiazepine prescription rates throughout the 15-years study period showed a modest increasing trend in the younger age group of 18-44 years old (AAPC=APC= 2.5, 95% CI: 1.7; 3.4). This result was attributed to a more pronounced increase in prescription rates in younger males of 18-44 years old (AAPC=APC= 4.5, 95% CI= 3.0; 6.0), since no significant changes in the same age group of females were observed in the period studied (APC= 0.8, 95% CI: 0.0; 1.7).

Figure1a. Short term Benzodiazepine prescription rates during study period stratified by gender and age group

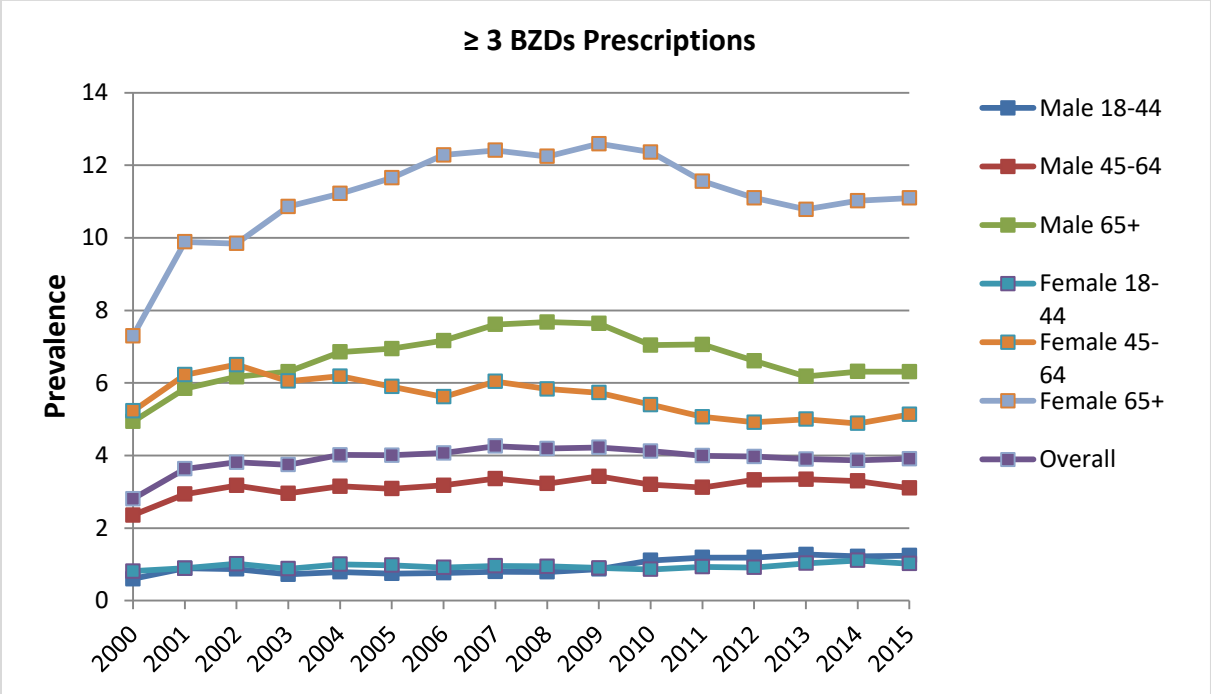


Similar to what we observed in the male younger age group of 18-44 years old, in the entire study period, males aged 45-64 years showed a significant increase, although smaller than that of the younger males, (AAPC=APC= 0.9, 95% CI: 0.1; 1.7). In contrast to males the trend was decreasing in females aged (45-64) years (AAPC=APC= -1.6, CI: -2.3; -0.9) (Table2).

In long term users, as it is illustrated in table 2 and Figure 1b, we found a dichotomous trend in benzodiazepine prescription rates in adults aged 65 years and above in the entire study period. The first trend which was observed between 2000 and 2007 was a pronounced increase (APC= 5.6, 95% CI: 3.6; 7.7). The second one was a modest decrease that was observed between 2007 and 2015 (APC=-2.6, 95% CI: -3.9; -1.3). In those older individuals no gender differences in prescription rates were observed. In females the first trend was a pronounced increase that was observed between 2000 and 2006 (APC= 7.0, 95% CI: 3.9; 10.2) and the second one was a slight decrease and was observed between 2006 and 2015

(APC= -1.8, 95% CI= -3.1; -0.5). In males the first trend was less pronounced than that of females and was observed between 2000 and 2007 (APC= 5.5, 95%CI= 3.8; 7.2). The second one was in the second period from 2007-2015 and showed a modest decrease (APC= -3.0, 95% CI; -4.0; -1.9).

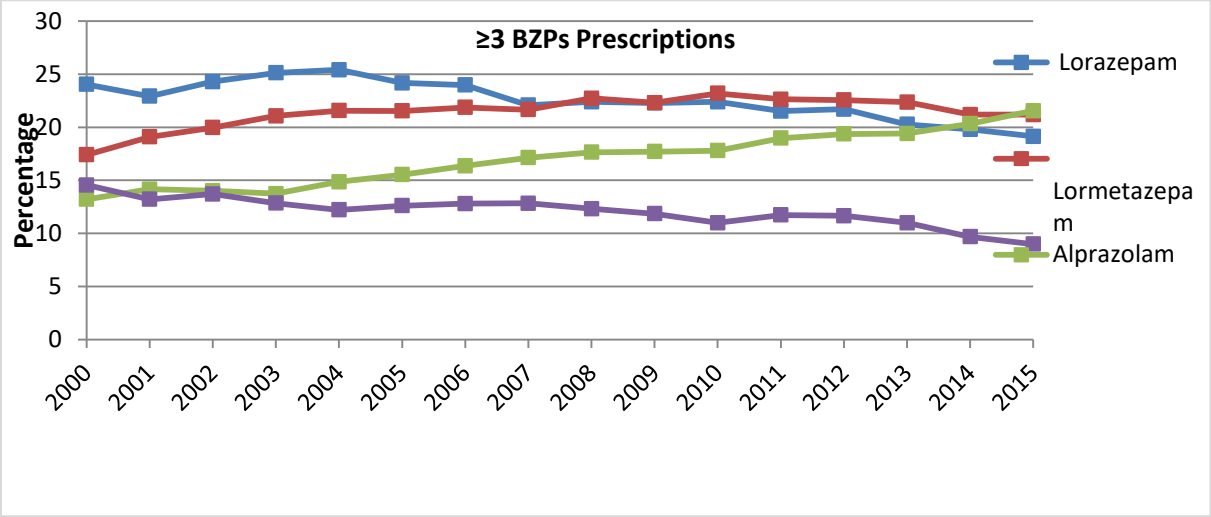
Figure 1b. Long-term Benzodiazepine prescribing trend during study period stratified by gender and age -group



The most frequently long term prescribed benzodiazepines

The most frequently prescribed benzodiazepine in 2000 was Lorazepam (fig 2). Lormetazepam accounted for 24% of the long term prescriptions in 2000, followed by Lormetazepam (17%), Bromazepam (14.5%), and Alprazolam (13%) respectively. In contrast to 2000 in which Alprazolam was prescribed the least, in 2015 Alprazolam was prescribed the most (21.5%) followed by Lormetazepam (21%) and Lorazepam (19%). As expected Bromazepam was prescribed the least in 2015 (8.9%) (Figure 2).

Figure 2. The most frequently long term prescribed benzodiazepines between 2000 and 2015



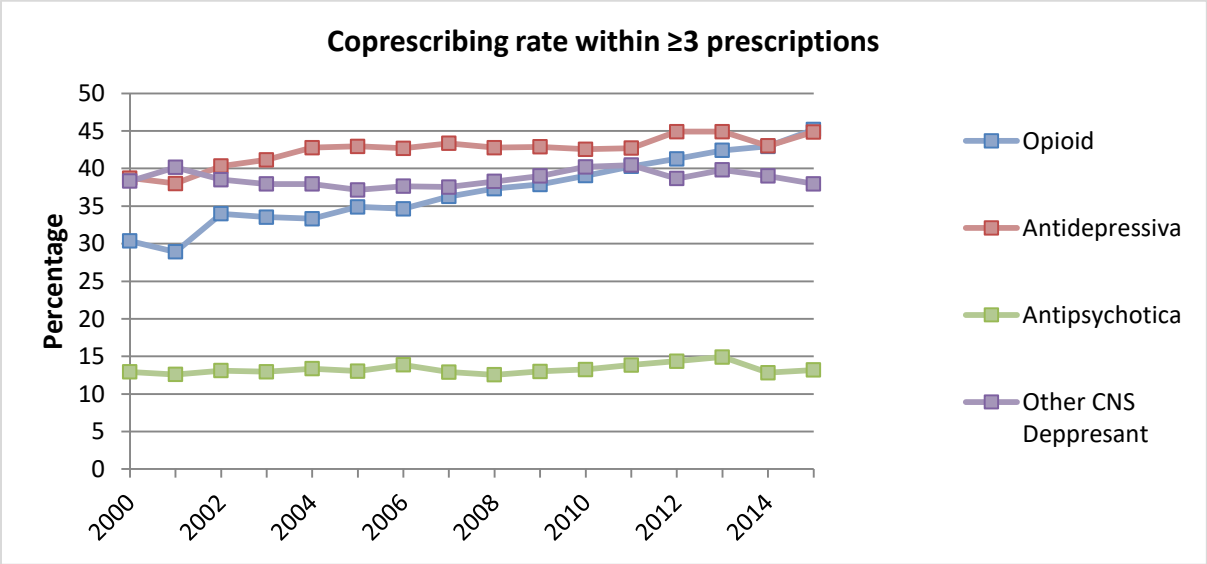
Indications for short- and long term benzodiazepine prescriptions

Looking at the indications for which BDZs were prescribed, we found that 28 % (n=1152) of the short-term users in 2000 received BDZs associated with back pain (table 1). This was significantly increased to 42% in 2015 (n=2221, $P < 0.001$). In long-term users prescription rate was increased from 33% (n=728) in 2000 to 48% (n= 1873) in 2015 (table1), showing that a large proportion of the benzodiazepine use was associated with back pain. With respect to indications other than back pain, we also observed the similar significant trends in prescription rates from 2000 to 2015 for both short- and long-term uses of BDZs. The increase was more remarkable among those with depression (26% in 2000 compared with 29% in 2015 for long-term users, P= 0.03). The least pronounced increases in long-term prescription rates were related to insomnia and anxiety respectively (from 7% in 2000 to 14% in 2015 for insomnia and from 5% in 2000 to 7% in 2015 for anxiety) (table1).

Concomitant use of benzodiazepines with other sedative/hypnotics

Overall co-prescription rates for Opioids, antidepressants and Z-drugs were significantly increased in 2015 compared with that in 2000. This increased co-prescription was observed in both short- and long-term users (table 1, Figure 3).

Figure3. Co-prescribing rates for Benzodiazepines with opioids and other psychotropic medications



As illustrated in table 1, in 2000, BDZs were co-prescribed with Opioids in 21% (n=868) and 30% (n=678) of the short- and long-term users respectively. This was significantly increased to 34% (n=1773) and 45% (n=1776) in 2015 for short- and long-term users respectively ($p < 0.001$ for each comparison). Interestingly increased Opioids prescription rate in long-term users was in line with the increased prescription rate of BDZs associated with back pain (leading indication for BDZS prescription) indicating that a great number of the patients received BDZs because of the back pain, while the current guidelines do not recommend BDZs for back pain relief.

In 2000 antidepressants were prescribed in 39% of the patients (n=865) who also received ≥ 3 prescriptions for BDZs. This was increased to 45% (n=1763) in 2015, ($P<0.001$) (table 1). Similar to increased co-prescription rates for opioids and antidepressants, we also found,

independent of the number of prescriptions, a significant increase in the proportion of the patients who received BDZs together with Z-drugs in 2015 in comparison with that in 2000 (n=137= 6% in 2000 vs n=395= 10% in 2015 for ≥ 3 prescriptions group, p<0.001)

Looking at the trends in concomitant use of benzodiazepines with other sedative/hypnotics in the entire study period, we found that between 2000 and 2015 benzodiazepines were in a sharp increasing trend co-prescribed with opioids (fig 3), similar to what we found in the serial cross-sectional analysis in 2000 and 2015. We also observed a slight increase in the rate of co-prescribing antidepressants with BDZs in long-term users (fig 3).

Discussion

In this study we used a large general practice database (Intego) to describe the evolution of benzodiazepine prescription by primary care physicians in the Flanders region of Belgium over a 15-year period starting from 2000. We found an overall prevalence of 3, 9% for long term benzodiazepine use in 2015 indicating a 1.4-fold increase in prescription from 2000. Different prescription patterns, however, were observed in different age and gender groups. Overall, while more women were prescribed BDZs in both 2000 and 2015, the prescription rate in females was decreased in 2015. In both study years and stratified by age group, we found that older adults aged 65 years and above made up the majority of the long term users. They were prescribed more BDZs in 2015.

However, looking at the trend in gender- and age-standardized prescription rates between 2000 and 2015 using joinpoint analysis we found a clear gender difference for younger and middle-aged adults below 65 years old. Younger males aged < 45 years showed a strong upward trend in long term benzodiazepine use over the 15-years study period. There was a slight increase in middle-aged males of 45-64 years old. In contrast to this latter group of males, middle-aged women showed a slight decrease in long term BDZs use over the 15-years

study period. In the older population, however, there was no gender difference. Indeed, we found a dichotomous trend for long term benzodiazepine use in both male and female older adults aged 65 years and above. The first trend, which was observed between 2000 and 2006-2007, showed a pronounced increase, whereas the second trend showed a slight drop that was observed afterwards (between 2006-2007 and 2015).

Regarding the indications for benzodiazepine prescription, we found that a relatively high percentage of the long term use of BDZs was related to back pain. The least pronounced increases in the prescription rates were related to insomnia and anxiety respectively. Interestingly, the increased opioid prescription rates in long-term users were in line with increased prescription of BDZs due to the back pain. This suggests that a great number of our patients received BDZs because of the back pain, while different clinical guidelines do not recommend BDZs for back pain relief.

Given different methodologies in studying benzodiazepine prescription patterns among physicians, for instance differences in the definition of long term users, the source/collection of data and the period examined, our study is not fully comparable with studies from other countries. Trying to make similar comparisons in terms of data source en examined periods, our findings are similar to those from Spain and the United States with respect to overall increasing prevalence of benzodiazepine prescription rates[1 21 2]. In the province of Seville in Spain a study showed that benzodiazepine consumption increased by more than 20% over a 10-year period (January 2006-December 2015) with a single joinpoint in March 2009[2]. In another serial cross-sectional study from the United States the authors, using nationally representative data, showed that the rate for benzodiazepine prescription increased from 3.8% in 2003 to 7.4% in 2015[21]. In addition, the indications for longer prescription periods were also similar to what we found in our cohort. In line with our findings, the study showed that benzodiazepine use associated with the chronic/back pain accounted for a greater percentage

of the benzodiazepine use compared with that for anxiety (2 times more than that for anxiety)[21].

Of interest in another study, aimed at comparing time trends in benzodiazepine prescriptions using different electronic databases but a common methodology, different prevalence rates were observed[22]. In this latter study prevalence rates of benzodiazepine prescription between 2001 and 2009 were investigated in 7 databases from 5 European countries including Denmark, Germany, The Netherlands, Spain and the United Kingdom. Despite the same study protocol and analysis, standardized prevalence rates were different across the aforementioned populations. Spanish (+13%) database and 2 databases from the United Kingdom (+2% and +8%) showed an increasing trend. In contrast, other databases showed decrease in prevalence rates with the most pronounced decrease in Danish database (-26%) and the least in one of the 2 databases from The Netherlands (-4%). Another database from The Netherlands showed a significant decrease of -22%, suggesting the effect of different populations even in the same country on the observed prevalence rates[22]. The authors of this study also concluded that inter-population differences as well as benzodiazepine-related factors may explain those differences[22].

In contrast to a pronounced gender independent increase in benzodiazepine prescription rates in older adults in the first half of the study period, in the second half we found a slight decrease. This decrease, however, should be interpreted with caution since in our study no electronic records of prescribed medications to older adults living in residential care centres were available. It should be mentioned that at least 20% (19.5% in 2015) of the population in Flanders of Belgium is aged 65 years and above[23]. Of this older population, 7% are living in nursing homes[23] suggesting that relatively a large number of older adults live in residential care centres for whom no electronic medication report was available in this study. Furthermore, high rates of benzodiazepine use have been reported in nursery homes in

Flanders[24]. In a cohort study of more than 650 healthy volunteers aged >65 years living in different nursing homes in Flanders in 2014, a high percentages (60%) used one or more benzodiazepines or benzodiazepine-related drugs. Lormetazepam was prescribed the most (54.8%) followed by Lorazepam (17.4%), and zolpidem (15.2%). Taken together these data suggest that the reported rate of benzodiazepine prescription in the older population of our study might be an underestimation.

Conclusion

In conclusion, although different age and gender groups showed different prescription patterns, prevalence of long term use of BDZs increased slightly during the 15-years study period. A large proportion of the long term use of BDZs was associated with back pain and depression, in line with a larger proportion of co-prescribing opioids and antidepressants with BDZs. Our findings point at the need to address the issue of increased long term use of BDZs.

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Appendices

Appendix 1

Positive advice ethical commission

KU LEUVEN

SCONE - Het platform voor stages en masterproeven

Geachte professor,
Beste student,

De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef integraal deel uitmaakt van een studie die reeds werd goedgekeurd door een erkend ethisch comité.

U hoeft bijgevolg geen nieuw dossier in te dienen in het kader van uw masterproef. Wel dient u het UZ/KU Leuven toe te voegen als nieuw deelnemend centrum aan het huidige dossier indien dit nog niet het geval was. Gelieve u bij het betreffende comité te informeren en u te conformeren aan de daar geldende procedures en hun adviezen te volgen.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij de goedkeuring om het onderzoek in het kader van de masterproef te starten.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet elke eerdere goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier bij het comité dat eerder uw dossier goedkeurde.

Veel succes!

Appendix 2

Masterpaper Protocol

MASTERPAPER PROTOCOL: RETROSPECTIVE STUDY

1. APPLICANTS

Protocol - full title	**Evolution of the Benzodiazepine Prescription by Primary care Physicians in Flanders: A registry-based study**
Version 1: Date submission	Date:21/05/2020
Version 2: Date resubmission	(to add in case of resubmission) Date:Click here to enter a date.
Version 3: Date third submission	(to add in case of third submission) Date:Click here to enter a date.
Principal Investigator – Promoter	Professor Catharina Matheï
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2. BACKGROUND AND RATIONALE

Benzodiazepines are widely prescribed by various health professionals including general practitioners. This is mainly because of the wide range of potential therapeutic options for those molecules including anxiety, insomnia, epilepsy, psychiatric disorders among others. Long term use of Benzodiazepines is, however, associated with many (potential) health risks in contrast to benefits from their short term-use. That is why different guidelines recommended short-term use of Benzodiazepines if there is an indication for which these medications should be prescribed. Different studies have been shown a wide range of health

issues in case of long-term use of Benzodiazepines. It has been documented that long term use of Benzodiazepines is associated with drug dependence, cognitive impairment, fall risk and resulting fractures, insomnia, and memory disorders especially in older populations (1-9) To reduce the long-term use of Benzodiazepines due to their long-term prescription, one potential point for intervention is the transition from short- to long-term use of these medications. Therefore, it is of utmost importance to know which factors can predict long-term use of benzodiazepines. Alternatively, one can compare the indications for short- and long-term Benzodiazepines' use. Given the higher risks associated with taking multiple medications that affect the CNS, we also investigated trends in co-prescribing benzodiazepines with other sedative medications including Opioids. Elucidating (co)prescribing patterns of benzodiazepines as well as indications for- and complications from their (mis)use can help us to better understand and as a result to address the issue of the increased use of benzodiazepines and their consequent complications.

3. STUDY OBJECTIVES

- To map the evolution of the Benzodiazepines prescription by primary care physicians in Flanders by analyzing the trend in age-standardized rates between 2000 and 2015
- To evaluate trends in BDZs co-prescribing with opioids and other CNS depressants
- To investigate the indications for short- and long-term use of benzodiazepine

Research questions:

Do general practitioners apply guidelines with respect to Benzodiazepines prescription? e.g:

- For which indications are Benzodiazepines prescribed?
    - What are the characteristics of patients who use benzodiazepines (age, gender, co-morbidity)?
    - How frequent general practitioners prescribe benzodiazepines?
    - Which benzodiazepines (short-acting versus long acting) do they prescribe?

4. RESEARCH METHOD

This thesis is a retrospective registry-based study based on the analysis of Intego databank. Using aforementioned databank we tried to answer research questions. Before that the research questions were formulated using a list of relevant ICPC-2 and ATC codes to extrapolate data from Intego databank.

The annual benzodiazepine prescription rates among adults (aged18 years) during the 15-year study period (2000-2015) were calculated in different age groups and gender. Analysis was done separately for patients who received a) less than 3 (short-term users) and b) more than two prescriptions (long-term users) for BDZs. We also did two cross-sectional analyses in years 2005 and 2015 with respect to indications and other parameters.

5. DATA COLLECTION

For the purpose of this thesis, data from Intego project was used. Intego which stands for "integrated computerized network" was established by the Department of General Practice of the KULeuven in 1990 (10). Therefore, it is a computerized morbidity registration network based on general practice data. The source of Intego data is information provided by a network of about 100 general practitioners. Those general practitioners work in around 50 practices with an optimal registration performance. Data provided by those practices are collected during their daily practices and contain some demographic, clinical and biomedical information (such as age, gender, weight, height, blood pressure and (new) diagnosis), laboratory tests, and electronic prescribed medications among others. Data registration occurs with use of computer-generated keywords in a predetermined field in the electronic health record. Each keyword is associated with a unique program-specific internal code and can be linked to classifications as International Classification of Primary Care (ICPC-2) for diagnosis, and WHO's Anatomical Therapeutic Chemical (ATC) for medications.

6. ANALYSIS

The annual benzodiazepine prescription rates among adults (aged18 years) during the 15-year

study period were calculated in different age groups: 18-44-, 45-64- and >64 years old and gender. Prescribing rates were calculated per 1000 patients who received less than three- or more than two- Benzodiazepine prescriptions per year. A repeated cross-sectional analysis, using Chi-square trend test, was conducted to investigate and compare the general benzodiazepine prescription trends in 2000 and 2015, indications for which benzodiazepines were prescribed as well as concomitant prescribed medications. This comparison could indirectly show us which factors were important in long-term use of Benzodiazepines

We also evaluated trends in benzodiazepine co-prescribing with Opioids and other CNS depressants

For the purpose of abovementioned analyses following data were extracted from Intego databank

The prevalence of both < 3 and ≥ 3 Benzodiazepine prescription (ATC codes NO5BA, NO5CD, NO3AE) in years 2005 and 2015 for the population of:

18-44 years old

45-64 years old

> 64 years old

18 years and older, and male

18 years and older, and female

18 years and older, and one of the following ICP codes (B74, (D74-75-76-77), R84, S77, T71, (X76-77), (U75-76-77))

18 years and older, and one of the following ICP codes (P29, P73, P75, P79, P80, P98, P99)

18 years and older, and one of the following ICP codes (N86, N87, N88, N99, N04, N06)

18 years and older, and one of the following ICP codes (Z04, Z08, Z27, Z28, Z29)

18 years and older, and the following ICP codes (P06, (P15, P18), P70, P74, P76, T90, K86, (L02, L03))

18 years and older, and the following ATC codes (N02, (N06A, N06AX, N06CA), N05A, N05C, N05CF)

Different Benzodiazepine type visit rate during the study period:

All benzodiazepines (overall) (N05BA, N05CD, N03AE)

Short/ intermediate-acting benzodiazepines: alprazolam (N05BA12), bromazepam (N05BA08), brotizolam (N05CD09), clotiazepam (N05BA21), loprazolam (N05CD11), lorazepam (N05BA06), lormetazepam (N05CD06), Oxazepam (NO5BA04)

Long-acting benzodiazepines: clobazam (N05BA09), clonazepam, clorazepaat(N05BA05), cloxazolam(N05BA22), diazepam (N05BA01)

Z-Drugs: N05CF

Co-prescribing rate for Benzodiazepines with Opioids and other psychotropic medications during the study period (between 2000 and 2015):

N02= Opioids

N06A, N06AX, N06CA= antidepressant

N05A - Antipsychotics

N05B - Anxiolytics

N05C - Hypnotics and sedatives (other CNS depressant)

To analyze the trend in age-standardized rates between 2000 and 2015, we used Joint point regression analysis. A joint point is a point in the trend curve where a statistically significant change in trend over time is observed. The trend analysis using the joint point regression model was performed using the SEER*Stat software (Joint point Trend Analysis software from the Surveillance Research Program of the US National Cancer Institute (available at http://surveillance.cancer.gov/joinpoint)).

7. DATA HANDLING AND MANAGEMENT

7.1 Data storage and management

This study is a retrospective cohort study which used Intego databank. The source of Intego data is information provided by a network of general practitioners. All the analyses were performed by an Intego analyst given me the results of the requested analyses.

7.2 Declaration of Confidentiality and Careful Management of Information and Personal Data

In the framework of his / her Master's thesis, the student(s) will have access to all kinds of data, information, results and documents, including personal data which is not exclusively limited to patient data (the "Information"). In order to ensure the confidentiality of this Information and the privacy of those involved, within the framework of his / her Master's thesis the student(s) should always deal with the Information with the greatest care and discretion.

Data collected in the framework of a Master's thesis, in particular research related to patients and including the collection and analysis of personal data, requires the utmost of care and discretion. Therefore, at all times the student must observe complete confidentiality with respect to the Information he / she has collected during the course of his / her Master's thesis.

In performing this research, the student(s) commit(s) him/herself to the following confidentiality

obligations:

- He / she accepts, during and after the completion of the Master's thesis, the obligation to strictly observe the confidentiality of the Information he / she has collected and the activities to which he / she has participated, and regarding the patients, healthy volunteers and the staff members with whom he / she comes into contact;

- He / she will only process and collect data that is relevant and necessary for his / her Master's thesis;

- He / she will not share information with persons not directly involved within the framework of his / her research;

- He / she will take all necessary steps to protect the confidentiality of Information and the privacy of those involved;

- He / she will handle with care and responsibility the Information and the access granted to him/her to information systems and digital media.

  All investigators shall treat all information and data relating to the study as confidential and shall not disclose such information to third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as participants' health and medical information, is subject to compliance with applicable personal data protection legislation.

8. APPROVAL

Hereby we confirm that data collection is performed with approval of the head of the respective unit(s) or department(s) where data collecting is taking place.

9. PUBLICATION POLICY

Publications will be coordinated by the Principal Investigator. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective journal.

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The investigator(s) and the institution(s) will permit study-related monitoring, audits, ethical review and regulatory inspections (where appropriate) by providing direct access to source data.

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